BET 5.16.02 3728
#7 PRIORITY Doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Jonathan Stanley Harold Denyer Anthony Dyche	Docket:	102199-100
Serial No.:	09/781,610	Art Unit:	3728
Filed:	February 12, 2001	Examiner:	Not Assigned
Assignee:	Medic-Aid Limited		
Title:	IMPROVEMENT IN AND RELATING TO DRUG DELIVERY APPARATUS		

Certificate of Mailing

Date of Deposit: March 13, 2002.
I hereby certify under 37 CFR 1.8(a) that this correspondence (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Signed: William A. Simons

Name: William A. Simons

CERTIFIED COPY OF PRIORITY APPLICATION

Commissioner for Patents
U.S. Patent and Trademark Office
Washington, DC 20231

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country:	Great Britain
Application No.:	0003197.1
Filing Date:	February 11, 2000

Applicant claims foreign priority benefits under 35 U.S.C. §119 of this application.

If the Examiner has any questions regarding this Certified Copy, please call the undersigned and a phone number given below.

Respectfully submitted,
Jonathan Stanley Harold Denyer, et al.

Date: March 13, 2002
Reg. No. 27,096

Signature of Attorney
William A. Simons
WIGGIN & DANA LLP
One Century Tower
New Haven, CT 06508-1832
Telephone: (203) 498-4502
Facsimile: (203) 782-2889

714101!.DOC\10706\45\328033.01

PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

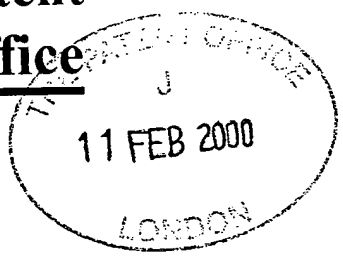
Signed Andrew Gerrey

Dated 22 FEB 2002

ts Act 1977
e 16)

BEST AVAILABLE COPY

The Patent Office



1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference P50015GB

2. Patent application number *(The Patent Office will fill in this part)* **0003197.1** 11 FEB 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Medic-Aid Limited
Town Quay House
7 Town Quay
Southampton
SO14 2PT
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation: United Kingdom

GB9258703

4. Title of the invention

Improvements in and relating to Controlling Drug Delivery Appatatus

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

WITHERS & ROGERS
Goldings House
2 Hays Lane
London
SE1 2HW

Patents ADP number *(if you know it)* 1776001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

5 Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	9
Claim(s)	-
Abstract	-
Drawing (s)	3

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Withers & Rogers Date 11 February 2000

12. Name and daytime telephone number of person to contact in the United Kingdom — Howard Wright 0171 663 3500

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500 505.*
b) *Write your answers in capital letters using black ink or you may type them.*
c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*
d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*
e) *Once you have filled in the form you must remember to sign and date it.*
f) *For details of the fee and ways to pay please contact the Patent Office.*

P50015GB
C:\Spec

IMPROVEMENTS IN AND RELATING TO CONTROLLING DRUG DELIVERY APPARATUS

This invention relates to the control of drug delivery apparatus, for example such apparatus for delivering a drug to a patient's lungs through inhalation.

A number of devices are available for delivering a drug into the lungs of a patient. A pneumatic or jet-type nebulizer is particularly effective in supplying an aerosolized drug for inhalation, but other types of nebulizers are also available, such as a ultrasonic type nebulizer in which the drug to be atomized is forced through a mesh by vibrating a piezo-electric crystal, whereupon the droplets passing through the mesh are entrained in the air being inhaled by the patient. The mesh gauge determines the size of the droplets which enter the air stream. Alternatively, dosimetric spacer can be used. When using a spacer, the drug is introduced into a holding chamber of the spacer, either in aerosolized form, or by loading the air within the holding chamber with the drug in powered form. The patient then breathes from the holding chamber, thereby inhaling the drug laden air. Such spacers are particularly effective when treating children or elderly patients, and for use with certain drugs. The drug is normally delivered over a number of breaths. Of course, the concentration of the drug in each breath decreases over time as a result of dilution caused by ambient air entering the holding chamber to replace the air being inhaled by the patient, and as a result of the deposition of the drug within the chamber.

As will be appreciated from this specification, the invention applies to all different types of drug delivery device.

When a doctor prescribes a particular drug for treatment of a patient, the patient not only requires a supply of the drug, but also requires a drug delivery apparatus, for example a nebulizer or a dosimetric spacer. In the case of a nebulizer, the prescribed amount of drug for a treatment is placed in the nebulizer, and in most cases, the patient inhales from the nebulizer repeatedly until the prescribed amount of drug has been delivered. Unfortunately, this is no guarantee of the patient receiving the required dose in his or her lungs. Most of

the drug tends to impact in the patient's airways before it reaches the lungs, and some of the drug is exhausted from the lungs on exhalation. Typically, about ten percent of the drug which is delivered by the atomizer reaches the lungs. However, there is a wide variation in the proportion of the drug which reaches the lungs of the patient since the effectiveness of the drug delivery depends on the way in which the patient uses the device. If the patient inhales deeply and regularly, then plenty of the drug will reach the lungs. However, for patients exhibiting symptoms of pulmonary disease, breaths will be shallower and treatment may be interrupted by symptoms of their disease such as coughing. This will substantially reduce the amount of the drug delivered to the patient such that they will not receive as much of the drug as their doctor intends.

More recently, the applicant for this patent has put on the market a nebulizer which calculates the dose of the drug which the patient receives in his lungs. The nebulizer is supplied to the patient pre-programmed with the dose of a particular drug which the patient requires. The patient is prescribed a particular drug, and before use the patient will insert the drug, usually in liquid form, into the nebulizer. The patient then starts inhaling from the nebulizer and the drug is delivered to the patient. The atomiser is arranged such that it only delivers the drug during the first fifty percent of the inhalation phase of the patient, and the flow rate of inhalation of the patient through the device is measured, and from this, the dose of drug received by the patient can be calculated. Once the pre-programmed dose has been delivered, the nebulizer will automatically stop atomizing the drug regardless of whether or not any drug remains within the nebulizer which has not been atomized. The atomiser must be reset before the next dose of the drug is delivered. This device is disclosed in Medic-Aid Limited's earlier patent publication (GB-A-2316323), and we hereby incorporate the information contained therein by this reference.

Whilst the applicant's product has significantly improved the accuracy of drug delivery, if the patient's doctor wishes to change the dose of the drug delivered to the patient, or to change the prescribed drug altogether, it is necessary to return the nebulizer for reprogramming, or to replace it with one with the correct drug and dose details.

In a known drug delivery system, the prescribed drug is supplied in individual drug vials, each of which contains the required drug for a single treatment. Thus, a number of vials will normally be supplied to the patient for use one at a time over a period of, say, one month. In that arrangement, each drug vial carries a bar code thereon such that, before each treatment, the bar code is read by a bar code reader on the atomizer to identify what the drug is which is to be delivered. However, the/bar code must be attached to each vial requiring increased manufacturing costs and also the carrying out of regulatory approval tests to ensure that the adhesives of the label and the dyes used will not contaminate the drug within the plastic vials or reduce the storage life of the product. Long term stability testing over two or three years is required.

According to another prior art arrangement, narcotic drugs are delivered using an atomiser for pain relief. In that case, it is clearly important to restrict access to the use of the drug delivery apparatus with that drug to the patient concerned. The patient is supplied with an I-button which is kept separate from the drug and the atomiser, and which must be touched against a contact surface on the atomiser in order to activate it for a treatment. The button is merely used as a key to unlock the atomiser for a single treatment.

According to a first aspect of the invention, a drug package comprises a plurality of drug vials containing drugs for delivery to a patient in a drug delivery device; and a data carrier including drug treatment information for use by the drug delivery apparatus. Preferably, the drug treatment information includes at least one of the following items of treatment information:

a. the dose of drug to be delivered,

b. the drug which is to be delivered,

c. the expiry date of the drug, and

d. the number of treatments in the package supplied with the data carrier.

Preferably, the drug delivery apparatus is one for delivering the drug in the inhaled air stream to the lungs. The drug delivery device may be one of a pneumatic nebulizer, a piezo-electric nebulizer or an ultrasonic nebulizer. The invention is not, however, limited to these types of nebulizer.

The data carrier is preferably in the form of a button. The data carrier may be moved to a receptive surface or region of the drug delivery apparatus in order to transfer the details the treatment into the nebulizer. Preferably, only one data carrier is supplied in the package, and each time a vial of drug is to be delivered, the data carrier is moved into the region of the drug delivery apparatus to transmit the treatment information to it. The data carrier will normally only transmit the treatment information to the apparatus on a limited number of occasions corresponding to the number of drug vials supplied in the package, or the apparatus will only allow a limited number of treatments to be delivered, corresponding to the number of drug vials.

Preferably, the data carrier is a radio frequency device which is powered inductively from a radio frequency transmitted within the body of the drug delivery apparatus. The data carrier will generate an r.f. signal in return which will be superimposed on the driving r.f. signal from the atomiser, and which is received and decoded by the atomiser.

In addition, it I preferred that information concerning a treatment be transmitted back to the data carrier where in it recorded. Once the pack is finished, the data carrier may be mailed back to the doctor, or transmitted electronically by telephone so that the doctor is able to view how the treatments have taken place and whether or not the patient has been using the drug delivery apparatus correctly.

Since the data carrier is supplied in or on the package with the vials of drug, minimal regulatory difficulties are encountered. In addition, if a patient tries to use an unauthorised drug in the device, the atomiser will not operate. This is important since some drugs, such as Dnase or A1At, which are protein based drugs, may be damaged of they are contaminated with other drug substances. An atomiser device should only be used for this one drug. In addition, of a drug formulation is not compatible with the plastics used to manufacture the delivery apparatus, if the drug has been identified to the atomiser, it will not operate.

As a result of the use of the data carrier, each vial can contain more drug than is expected to be used so as to allow for inefficiency in the patient's breathing patterns, such as in a

MDI spacer system or to pediatric patients. In addition, the use of the vials containing larger amounts of a drug can be supplied for different treatments. The treatment information with the data carrier controls the dose of the drug delivered. Thus, a single vial size of drug can be manufactured and sold, but the size of dose can vary widely depending on the dose information carried by the treatment information. This results in economies of scale and reduces regulatory submissions.

According to a further aspect of the invention, a drug delivery apparatus includes a delivery portion for delivering a drug to a patient; an input for receipt of treatment information for each treatment to be administered to a patient; and a nebulizer controller for controlling the amount of drug delivered to a patient on the basis of the treatment information received. Preferably, the input is a radio frequency input which receives the treatment information from a data carrier at radio frequency. Preferably, the input is additionally arranged to transmit completed treatment information to the data carrier for recordal.

Preferably, the atomiser includes an authorisation portion which prevents atomization if any of the treatment information, such as the expiry date of the drug, indicates that the drug is not suitable for delivery.

According to a further aspect of the invention, an electronic data carrier for use with a drug delivery apparatus comprises a memory for holding treatment information concerning the use of the drug delivery apparatus in delivering a specified drug; and an output for transmitting treatment information to the drug delivery apparatus.

According to a further aspect of the invention, a drug delivery system includes a drug delivery apparatus for delivering a specified drug; and a electronic data carrier containing treatment information relating to the specified drug, the data carrier including an output for transmitting treatment information to the drug delivery apparatus before each treatment with the specified drug whereby the drug delivery apparatus delivers the specified drug in conformity with the treatment information.

According to further aspect, a method of operating a drug delivery apparatus comprises:

supplying a number vials of a drug for use with the drug delivery apparatus;

supply for a data carrier including treatment information;

transmitting treatment information from the data carrier to the drug delivery apparatus;

placing an amount of the drug in the drug delivery apparatus; and

delivering the drug in accordance with the treatment information from the data

Embodiments of the present invention will now be described with reference to the accompanying drawings by way of example only:

Figure 1 shows an atomiser for delivery of a drug, including a receptive region, together with a data carrier in the form of a button;

Figure 2 shows part of a flow diagram of operation of the nebuliser shown in Figure 1;

Figure 3 shows the remainder of the flow diagram shown in Figure 2.

Referring to Figure 1, a nebuliser 10 is shown including a body 1 and a mouth piece 2 through which a patient breathes to receive an atomised drug during his inhalation. In addition, the nebuliser includes a display 3 for displaying information concerning the use of the machine and the treatment being delivered, and an input 4 in the form of a region in which a data carrier in the form of a button 5 may be placed in order to transmit information concerning the treatment into the device 10.

In this case, the button includes a small microchip to which is connected an aerial. The atomiser 10 includes a radio frequency transmitter connected to a further aerial for generating a radio frequency signal. When the button 5 is placed in the region 4, the aerial within the button receives the radio frequency signal and generates electric power to operate the microchip. The microchip is then caused to generate an additional RF signal through the aerial in the button which contains treatment information. This is detected within the nebuliser, so that the nebuliser receives treatment information from the button. In addition, the nebuliser can generate an additional RF signal to download information concerning actual treatments on to the button so that the button may store information concerning treatment which may be read and analysed later.

Referring to Figures 2 and 3, a flow diagram is shown which indicates the operation of the drug delivery apparatus 10, and its operation in connection with the data carrier 2. Starting at the top of Figure 2, the logic operations of the drug delivery device 10, which is in this case is a pneumatic jet nebuliser starts at 101. First, the question 102 is asked whether or not compressed air is being received by the device. Since it is a pneumatic nebuliser the atomisation is driven by compressed air. It cannot operate until a supply of compressed air is received. Once compressed air is received, the device checks the battery to ensure that sufficient power is supplied to the device. The battery level is indicated to the patient on the display 3. The next step is to calibrate the sensor. The operation of this drug delivery device requires that the air flow through the device is known, firstly to indicate when a patient starts to inhale whereby the drug may be delivered, and secondly to calculate the dose delivered since the dose delivered is dependent on the flow rate through the device.

The next step is to calibrate the sensor as shown in step 104. Calibration is automatic, but if calibration fails, the device is switched off, and that failure is indicated to the patient. The next step, 105 is the entry into the drug delivery device of treatment information. The patient is given a period of thirty seconds in which to enter the treatment information by placing the data carrier 5 in the region of a reader 4 so that the treatment information may be downloaded. Once that treatment information is downloaded, the drug delivery apparatus checks that it has not already delivered all of the supplied doses of that drug. Provided that there are sufficient doses left, then drug delivery can begin.

Referring to Figure 3, which is a continuation of the flow diagram of Figure 2, the presence of compressed air is again checked at 106, and provided that it is on, it will wait for the patient to start inhaling. Provided that the patient inhales strongly enough, the first three breaths are measured to identify the average duration of inhalation, and the drug is then delivered into a subsequent breath for the first 50% of that breath, calculated by averaging the previous three inhalation durations. During treatment, the dose delivered by the drug delivery apparatus is continually calculated. Once the total dose reaches that which the patient is supposed to receive, on the basis of the treatment information supplied by the data carrier, an audible sound is generated, and the device is switched off. In addition,

information concerning the treatment which has been carried out can be downloaded on to the data carrier after the treatment, or before the next treatment is started. Furthermore, on completion of delivery of a dose, the drug delivery apparatus decrements the number of treatments left to be supplied by the package of drug associated with that data carrier.

The data carrier includes a number of data fields which are programmed into the carrier before it is inserted into a package of drug. This includes the number of treatments which can be derived from that drug package, a security code or access code whereby the security code of the data carrier identifies to the drug delivery apparatus so that it may only be used to deliver one set of treatments corresponding to the package of drug with which it is supplied. The data carrier also includes a drug identification, the dose to be administered in each treatment, and the expiry date of the drugs. In addition, if the data carrier is used to record the delivery of treatments, the drug delivery apparatus can download information on to the data carrier, including the serial number of the drug delivery apparatus in order to identify the machine and the patient, the number of treatments used, and other information concerning the treatments.

A telephone interface can be supplied whereby the information downloaded on to the data carrier from the drug delivery apparatus may be passed down a telephone line to the manufacturer or the doctor. It would identify the type of drug delivery apparatus, its serial number, the drug identification, the number of treatments of drug used, and any other useful information. Of course, the data carrier could also be mailed to the manufacturer, or to the doctor.

The use of the data carrier in this way has a number of different advantages. Firstly, it can prevent the use of unauthorised drugs in that drug delivery apparatus. This is advantageous for two reasons. Firstly, protein based drugs as Dnase or A1AT may be damaged if they are contaminated with other drug substances. Therefore, any drug delivery apparatus delivering one of these drugs should only be used for that one drug, and no other. In addition, the dose programmed into the drug delivery apparatus for a different drug may not be appropriate for all drug substances. Thus, the chance of the wrong dose being delivered to the patient is minimised. Also, some drugs may not be compatible with the

drug delivery apparatus concerned, for example with the plastics used to manufacture the device.

In addition, rather than the amount of drug delivered being controlled by the nominal volume drug in the phial, they are controlled by the dose treatment information in the data carrier. This is important since it allows more drug to be included in the vial than is normally needed to take account of inefficiency in the patient's breathing patents. It also means that different drug doses can be prescribed to the patient using the treatment information in the data carrier, but that one vial concentration can be manufactured and sold for all of these different doses, thus optimising economies of scale and reducing regulatory submissions. In the past, it would have been necessary to supply different concentrations or different volumes of a drug depending on the amount prescribed. The use of the data carrier means that fewer volumes and concentrations of a drug need to be manufactured.

The data carrier is also able to record information concerning patient compliance with his regimen, and can even drive a direct prescription. A doctor can be confident in the information received from the drug delivery apparatus which is recorded on the data carrier. The doctor does not need to rely on the patient's own reports of compliance nor their inhalation efficiency.

Since the data carrier is supplied with a number of vials of drug, different styles of packs can be used for different therapeutic applications. Some drugs must be supplied in a plastic unit dose phial, and others must be supplied in two-part packages for reconstitution at the point of use. Both of these drug vials can be accommodated because the data carrier is attached to the outside of the box, and contains the dosing information for the whole pack of the drug, typically one month. It is not attached to individual drug vials, and minimises the packaging, regulatory and development requirements for integrating the drugs into the drug delivery system. It avoids potential contamination problems on drug packs, which is a significant issue where labels or printing are applied to plastic vials. Lengthy stability tests are required to ensure there is no leaking of dyes or adhesives into the drug of the storage life of the product, which may be up to two years.

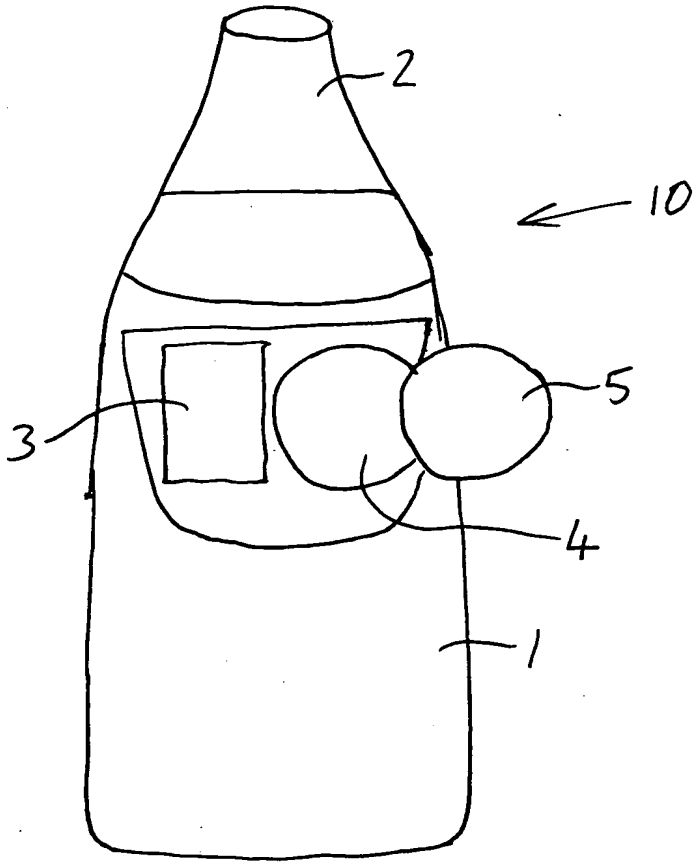


FIG. 1

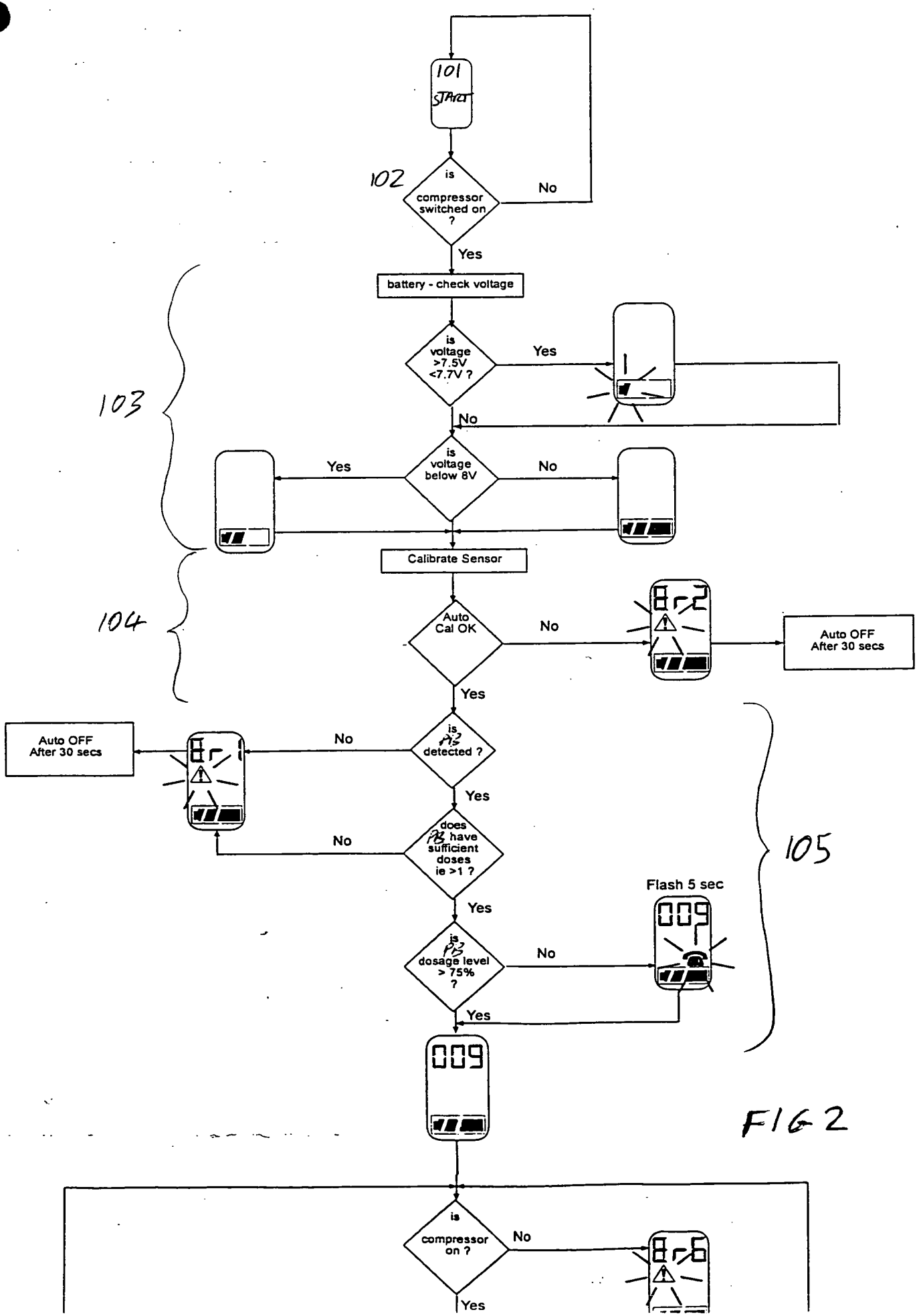

101
START
102
is compressor switched on ?
No
Yes
battery - check voltage
is voltage >7.5V <7.7V ?
Yes
No
is voltage below 8V
Yes
No
103
Calibrate Sensor
104
Auto Cal OK
No
Br2
Auto OFF After 30 secs
Yes
is P3 detected ?
No
Br1
Auto OFF After 30 secs
Yes
does P3 have sufficient doses ie >1 ?
No
Yes
105
Flash 5 sec
009
is P3 dosage level > 75% ?
No
Yes
009
is compressor on ?
No
Br6
Yes

FIG 2

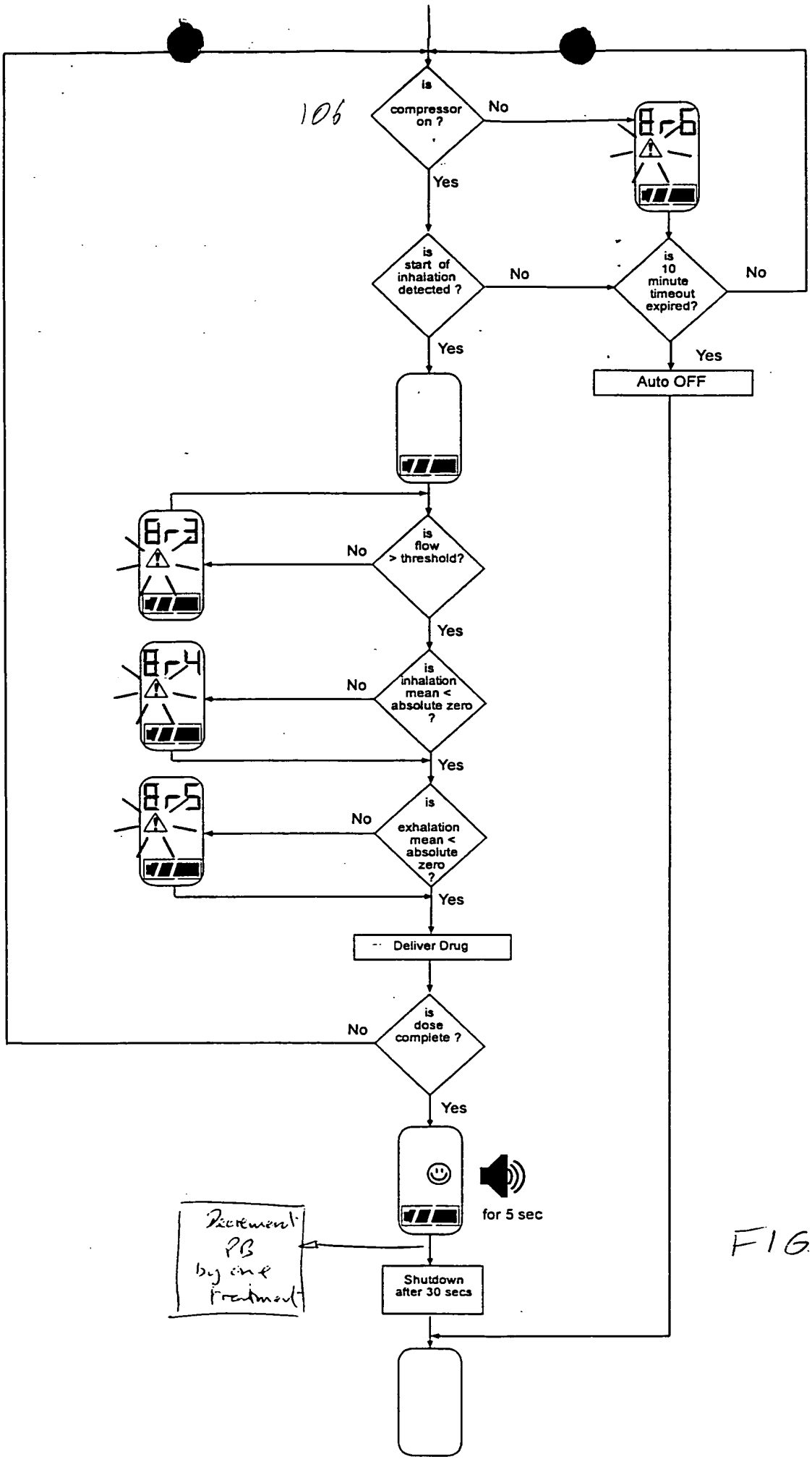

106
is compressor on ?
No
Yes
Br6
is start of inhalation detected ?
No
is 10 minute timeout expired?
No
Yes
Yes
Auto OFF
Br3
is flow > threshold?
No
Yes
Br4
is inhalation mean < absolute zero ?
No
Yes
Br5
is exhalation mean < absolute zero ?
No
Yes
Deliver Drug
is dose complete ?
No
Yes
for 5 sec
Shutdown after 30 secs

FIG 3